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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,598	01/06/2000	A. Gururaj Rao	5718-16A	1892
29122	7590	02/10/2004	EXAMINER	
ALSTON & BIRD LLP PIONEER HI-BRED INTERNATIONAL, INC. BANK OF AMERICA PLAZA 101 SOUTH TYRON STREET, SUITE 4000 CHARLOTTE, NC 28280-4000			KERR, KATHLEEN M	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/478,598

Applicant(s)

RAO ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 58,60-65,67-69,71,75-79,82,97-105 and 125 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 58,60-65,67,69,71,75-79,82,97-105 and 125 is/are rejected.
- 7) ☒ Claim(s) 68 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8/14/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on October 15, 2003), Applicants filed a response and amendment received on December 15, 2003. Said amendment cancelled Claims 54-57, 70, 80, and 119-124 and amended Claims 58, 65, 67-69, 71, 82, 97, 105, and 125. Thus, Claims 58, 60-65, 67-69, 71, 75-79, 82, 97-105, and 125 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. non-Provisional Application No. 08/988,015 filed on December 10, 1997.

Drawings

3. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Information Disclosure Statement

4. Upon the receipt of the fee for the information disclosure statement filed August 14, 2003, the IDS has been considered as noted by the Examiner's initials on the attached copy.

Withdrawn - Claim Objections

5. Previous objection to Claim 57 for having improper form is withdrawn by virtue of Applicants' cancellation of said claims.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

6. Previous rejection of Claim 123 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicants' cancellation of said claim.
7. Previous rejection of Claims 57, 58, 60-65, 67, 72, and 119 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicants' amendment and/or cancellation of said claims.
8. Previous rejection of Claim 65 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant's amendment to Claim 58 (the parent claim).

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

9. Previous rejection of Claims 54, 57, 58, 60-65, 67, 69, 72, 75-80, 82, and 119-124 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicant's amendment amending the claims to using sets of antibodies, which methods are described in the specification as originally filed.
10. Previous rejection of Claims 54-57, 68 and 119-124 under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of alteration of at least 10% of the amino acid content of the protein, is withdrawn by virtue of Applicants' cancellation or amendment of said claims.

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11. Previous rejection of Claims 54-57, 69-72, 75-80, 82, and 120-124 under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of using interacting molecules, even specifically antibodies, with *any* protein of interest, is withdrawn by virtue of Applicant's amendment limiting to using vegetative storage protein.

12. Previous rejection of Claims 54, 57, 58, 60-64, 68, 69, 72, 75-80, 82, and 120-124 under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of using *any* interacting molecules is withdrawn by virtue of Applicants' cancellation of said claims and/or their amendments to methods using only antibodies as interacting molecules.

13. Previous rejection of Claims 54-58, 60-65, 67, 68, 70-72, 80, and 119-124 under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of using a set of antibodies to determine VSP protein conformation, is withdrawn by virtue of Applicants' amendment and/or cancellation of said claims. The pending claim language of Claim 58 no longer requires that the antibodies used "determine" a conformation, but merely ---assessment--- of conformation is required and antibodies are capable of that. However, amended Claims 69 and 97 have slightly different language that require antibodies to ---identify--- native conformation which still lacks enablement for the reasons noted below.

Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

14. Previous rejection of Claims 67, 82, and 125 under 35 U.S.C. § 112, first paragraph, enablement, is altered to a scope of enablement rejection and maintained herein. While the specification enables methods of maintaining a particular antibody-assessed conformation when

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VSP β is mutated to the extent of 8.25%, the specification does not enable maintaining conformation at any great extent to which the claim is also drawn. Since the claim limits to “at least 8.25%” (emphasis added), only a single embodiment of this large genus is enabled. Applicants’ arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue that the scope of “at least 8.25” is enabled by the single embodiment noted by the Examiner to be enabled. The Examiner disagrees with this assessment for the following reasons previously of record.

“The example in the specification changes the content by 8.25%. Description of more extensive mutants is found (see Tables), but none are brought to fruition. It is wholly unpredictable whether or not the native conformation (or even a conformation recognized by the monoclonal antibody described) can be maintained with such extensive modification to the small protein sequence. On page 16 of the specification, it is noted that 51 out of 218 amino acid positions are postulated for mutation to hydrophobic residues and its “possible” that the VSP protein “might tolerate” all of said changes. The state of the prior art is extensive with numerous examples of alteration of amino acid content, but none to the extent of [greater than 8.25%] 10% of the amino acid composition while maintaining the native conformation.”

15. Previous rejection of Claims 69, 75-79, 82 and 97-105 and 125 under 35 U.S.C. § 112, first paragraph, enablement, due to the requirement of using a set of antibodies to assess mutated vegetative storage protein as native conformation or not, is maintained. Applicants present no arguments other than the amendment has obviated the rejection. The Examiner suggests adopting claim language such as that found in Claim 58 to overcome the instant rejection.

NEW ISSUES

Claim Objections

16. Claim 68 is objected to for depending from a rejected claim

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 67, 82, and 125 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of “**at least 8.25%** of the total amino acid content of the protein” (emphasis added) is considered new matter.

As previously noted by the Examiner, “[t]he instant specification describes a single example related to the pending claims wherein vegetative storage protein- β (VSP β) from *Glycine max*, a 218 amino acid protein, is mutated to increase its methionine content by 18 methionines (VSP β -met10); this represents a change in amino acid content of 8.25%, not at least 10%.” While the example teaches the invention of a method that alters the amino acids by *exactly* 8.25% (a single embodiment), neither this example nor elsewhere in the specification teaches the claimed scope of the invention, that is 8.25% *and greater*. Thus, the scope of the claimed

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invention is not supported in the specification as originally filed. Applicants are required to delete the new matter or cite clear support (page and line number) for the amendment.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 58, 61, 62, and 67 are rejected under 35 U.S.C. § 102(b) as being anticipated by Falco *et al.* (USPN 5,559,223). The instant claims are drawn to methods of altering the amino acid content of a vegetative storage protein by substitutions at sites determined by homology modeling, wherein the alterations increase nutritionally essential amino acid content by at least 5% and wherein nutritionally essential amino acids represent at least 8.25% of the total amino acid content of the protein.

Falco *et al.* teach altering synthetic seed storage proteins, like SSP(5) (see Table 3 in column 14), to increase nutritionally essential amino acid content and produce proteins like SSP(8). Falco *et al.* teach chemically synthesizing peptides like SSP(5) and SSP(8) and assessing their conformations using antibodies (see columns 28-31). Said alterations were chosen by virtue of homology alignments. Said alterations increase the essential amino acid content from 57% for SSP(5) to 71% for SSP(8), which increase is about 14% (see Table 3, for example SSP(5) (SEQ ID NO:2) relative to SSP(8) (SEQ ID NO:4), positions 7, 14, and 28).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

19. Claims 58, 60-62, 67, 71, 97-102 and 125 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* in view of Goldberg. The instant claims are drawn to methods of altering the amino acid content by increasing the levels of methionine of a vegetative storage protein by substitutions at sites determined by homology modeling, wherein the alterations increase nutritionally essential amino acid content by at least 5%, wherein nutritionally essential amino acids represent at least 8.25% of the total amino acid content of the protein, and wherein the conformation (structure) of the altered protein is assessed by binding of monoclonal antibodies.

Dyer *et al.* teach altering the primary structure of phaseolin, a seed storage protein, to enhance the methionine content of the protein to thereby enhance its nutritional value (see Abstract and page 665). Dyer *et al.* utilize specific knowledge of the protein's structure for determination of the most effective sites for insertion of methionines to cause the least perturbation on the overall structure of the protein; this specific knowledge is a form of secondary structure prediction (see Figure 1). Dyer *et al.* teach "increasing by tenfold the methionine content from the original 3 to 33 per 397 amino acid residues of the mature phaseolin polypeptide (see page 667, right column), which increase represents essential amino acids as 8.3% of the total protein. Dyer *et al.* also teach assessing the altered protein's structure using

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thermal and urea denaturation monitored by circular dichroism (see page 669 and page 673).

Dyer *et al.* do not teach assessing the altered protein's structure using monoclonal antibody binding assays.

Goldberg teaches how effective antibodies are in assessing protein conformation.

Particularly, Goldberg teaches that monoclonal antibodies are good conformational probes useful in assessing protein folding.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Dyer *et al.* and Goldberg to practice methods of altering seed storage proteins wherein antibodies, and not CD spectra, as used to assess protein conformation because in Goldberg and throughout the art, antibodies are known to recognize particular protein conformations specifically. One would have been motivated to practice such methods because antibody binding is easily testable and many antibodies are publicly available for seed storage proteins. One would have had a reasonable expectation of success that antibodies could substitute for CD spectra in the methods of Dyer *et al.*, at least to the extent required by the instant claims, because antibodies are well-known to be capable of recognizing gross protein conformation.

The Examiner notes that rejection of Claim 97 and dependent claims herein is set forth conditionally as if an amendment to the "assessing" step recommended above by the Examiner to overcome the full enablement rejection has been enacted by Applicants. The Examiner also notes that an analogous art rejection to this one was set forth previously in prosecution (see Paper No. 20 mailed November 19, 2000).

20. Claims 63-65 and 103-105 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* in view of Goldberg and in view of Arnold *et al.* The instant claims are drawn

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to methods of increasing the nutritional value of a native vegetative storage protein by altering its sequence wherein the conformation (structure) of the altered protein is assayed by binding of monoclonal antibodies and wherein the alterations are made randomly using DNA shuffling.

Dyer *et al.* teach as described above. Dyer *et al.* do not teach using random mutagenesis methods to produce methionine-enhanced phaseolin.

Goldberg teaches as described above.

Arnold *et al.* teach the use of random point mutagenesis, and specifically DNA shuffling, followed by screening for optimizing industrial proteins (see Abstract and page 8).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Dyer *et al.*, Goldberg, and Arnold *et al.* to practice methods of altering seed storage proteins wherein antibodies, and not CD spectra, as used to assess protein conformation after random mutagenesis because in Goldberg and throughout the art, antibodies are known to recognize particular protein conformations specifically and because random mutagenesis is more applicable to the vast majority of seed storage proteins whose homologies and/or secondary structures are less well-known. One would have been motivated to practice such methods because antibody binding is easily testable and many antibodies are publicly available for seed storage proteins and because random mutagenesis is more easily practiced than directed mutagenesis. One would have had a reasonable expectation of success that antibodies could substitute for CD spectra on the methods of Dyer *et al.*, at least to the extent required by the instant claims, because antibodies are well-known to be capable of recognizing gross protein conformation. One would have had a reasonable expectation of success that random mutagenesis would produce the desired mutants because nutritionally valued amino acids are common (9 out of 20).

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The Examiner notes that rejection of Claim 97 and dependent claims herein is set forth conditionally as if an amendment to the “assessing” step recommended above by the Examiner to overcome the full enablement rejection has been enacted by Applicants. The Examiner also notes that an analogous art rejection to this one was set forth previously in prosecution (see Paper No. 20 mailed November 19, 2000).

Summary of Pending Issues

21. The following is a summary of the issues pending in the instant application that MUST be addressed in response to the instant Office action:

- a) Claim 68 stands objected to for depending from a rejected claim.
- b) Claims 67, 82, and 125 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.
- c) Claims 67, 82, and 125 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.
- d) Claims 69, 75-79, 82 and 97-105 and 125 stand rejected under 35 U.S.C. § 112, first paragraph, enablement.
- e) Claims 58, 61, 62, and 67 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Falco *et al.* (USPN 5,559,223).
- f) Claims 58, 60-62, 67, 71, 97-102, and 125 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* in view of Goldberg.
- g) Claims 63-65 and 103-105 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* in view of Goldberg and in view of Arnold *et al.*

Conclusion

22. Claim 68 is objected to. Claims 58, 60-65, 67, 69, 71, 75-79, 82, 97-105, and 125 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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February 3, 2004